UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/829,674	04/22/2004	Anna Helgadottir	30847/2048-004	6838

4743 7590 04/16/2007

MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE, SUITE 6300
SEARS TOWER
CHICAGO, IL 60606

EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/829,674	HELGADOTTIR, ANNA	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-66* is/are pending in the application.

4a) Of the above claim(s) *62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61 and 63-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed January 26, 2007. Currently, claims 61-66 are pending. Claim 62 has been withdrawn as drawn to non-elected subject matter.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

3. Any objections and rejections not reiterated below are hereby withdrawn.

a. The written description rejection has been withdrawn in view of the amendments to the claims to require particular polymorphisms.

Maintained Rejections

Election/Restrictions

4. Applicant's election with traverse of Group I, Claims 1-4, 33-60, namely SG13S32 allele A and SG13S114, allele T in the paper filed May 3, 2006 is acknowledged.

The response asserts the markers and haplotypes are related insofar as they pertain to the same gene. The response further asserts the polymorphisms are located within the same FLAP nucleic acid and involve the use of polymorphisms and haplotypes to predict risk of the same disease state, susceptibility to myocardial infarction or stroke. This argument has been thoroughly reviewed but not deemed persuasive because multiple genes are related to myocardial infarction or stroke, including FLAP and phosphodiesterase 4D. Moreover, the instant specification teaches

that not all of the polymorphisms are associated with myocardial infarction or stroke (see page 83 of the specification). Thus there is no common utility. Moreover, the claims are drawn to the differences, i.e. the polymorphisms in the FLAP gene, and not the common structural features of the FLAP gene. Thus, there is no common structural feature for these polymorphisms either.

The response further asserts that the search of the claimed polymorphisms and haplotypes is not unduly burdensome. The response appears to assert that a search of SEQ ID NO: 1 is the only search required. This argument has been reviewed, but not deemed persuasive because the instant claims do not require SEQ ID NO: 1. The claims are drawn to the FLAP gene which may be any of a variety of genes. Moreover, the claims are not drawn to normal FLAP gene, but variants of the FLAP gene. Thus, a search for the normal FLAP gene would not be complete search. Furthermore, a search for each of the distinct haplotypes and polymorphisms requires a search in the literature for polymorphisms, variants, alleles etc. The polymorphic data of many genes is not placed in abstracts but rather in tables in the body of the article. Thus each article needs to be considered to provide a thorough search. It is noted that the numbering system of many of the genes is not consistent and thus provides added consideration and search for determining the presence of polymorphisms.

[redacted]

[redacted]

include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Drawings

5. The drawings are acceptable.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Newly added Claims 61, and 63-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman.

They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Newly added Claims 61-66 are drawn to a method of assessing a susceptibility to myocardial infarction or stroke in a human by screening nucleic acid of the individual to determining whether the nucleic acid comprises FLAP haplotype that comprises polymorphisms SG13S114T; SG13ZS32A; SG13S25G; SG13S89G wherein the presence of the haplotype is indicative of elevated susceptibility to myocardial infarction and wherein the absence identified the individual as not having the elevated susceptibility to MI or stroke.

The nature of the invention, therefore, requires the knowledge of predictive associations between the haplotype in any FLAP nucleic acid and susceptibility of myocardial infarction or stroke.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

Zee et al. (as cited in the Declaration filed 1/26/07; Stroke, Vol. 37, 2007-2011, 2006) teaches genetic variants of ALOX5AP) and HapA in myocardial infarction and stroke. Zee found no evidence for an association of the specific Icelandig haplotypes tested with risk of incident MI nor ischemic stroke in non-Icelandic study (abstract).

Moreover, Meschia et al. (Ann Neurology, Vol. 58, pages 351-361, 2005) teaches that there was no evidence of association between variants of ALOX5AP and ischemic

stroke. Hap A was not a risk factor for stroke in a British population but a different ALOX5AP (FLAP gene) haplotype (Hap B) was positively associated with stroke (page 351, col. 2). Meschia further continues that there was no evidence supporting linkage of either ALOX5AP or PDE4D with ischemic stroke susceptibility in these data (page 354, col. 1). As seen in Table 4 providing the analysis of ALOX5AP SNPs and association, no significant results were obtained (page 357).

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

The art teaches that presence of SNPs in the same gene does not indicate that

each of the genes is associated with the same diseases. Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpkl5 and cadpkl6 are not associated with the disease, however cadpkl7 has a p-value of less than 0.05, therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease.

Guidance in the Specification.

The specification provides no evidence that the skilled artisan could practice the claimed invention as broadly as claimed. The specification teaches that 49 markers were tested individually for association to the disease (page 83). Three SNPs showed nominally significant association to MI (page 83). Table 4 illustrates the nominal association of three SNPs. Further the specification concludes that "after adjusting for the number of markers tested, these results were not significant." The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied.

With respect to haplotypes, the instant specification provides Table 5 which is an analysis of 21 SNPs organized into haplotypes which are significantly associated with Icelandic MI patient. Table 7 illustrates 5 haplotypes over 10 SNPs which are each

associated with Icelandic MI patients. The claims have been amended to read that "the absence of the haplotype identified the individual as not having the elevated susceptibility to MI or stroke. This newly added recitation is inaccurate. The specification asserts that the rest of the table provides haplotypes, i.e. the absence of HapA, however confers elevated susceptibility to MI. Thus, the absence of the recited haplotype does not identify the individual as not having the elevated susceptibility to MI. Moreover, additional factors including other genes and environmental conditions create an elevated susceptibility to MI. The HapA haplotype is not the causative haplotype. It would require an undue amount of experimentation to determine how the absence of the HapA haplotypes identified individuals as not having elevated susceptibility to MI or stroke.

Moreover, the claims remain drawn to both myocardial infarction and stroke. Table 4 is directed to MI as is Table 5. The specification only analyzes the A4 haplotype with stroke. Moreover, it is noted that TIA is not significantly associated with Haplotype A4 (see page 88). Moreover as discussed above, Hap A was not a risk factor for stroke in British population (see Meschia). Thus, given the teachings in the specification and the art, it is unpredictable to associate haplotype A with stroke absent further unpredictable and undue experimentation. The skilled artisan would be required to perform trial and error experimentation to determine whether specific polymorphisms or haplotypes are associated with stroke. The outcome of such research cannot be predicted and such further research and experimentation are both unpredictable and undue.

The claims are drawn to any population of individuals. The claims encompass humans of different ethnicities. Further research and experimentation which is unpredictable and undue would be required to determine whether the skilled artisan

would use the claimed invention as broadly as claimed. Moreover, within the human individuals, there is inter-ethnic variability (see Meschia and Helgadottir). The post-filing date art supports the position that variants within different ethnicities confers different risks. It is unpredictable given the teachings in the specification directed only to Icelandic human patients and the post filing date art of Meschia and Helgadottir that all ethnicities share the same risk and ability to diagnose susceptibility to myocardial infarction or stroke.

Each of these concerns would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where there is no clear association between polymorphisms and a disorder, the broad scope of the claims may not be practiced without further unpredictable and undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner

that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The declaration presented by Dr. Anna Helgadottir has been thoroughly considered.

The response traverses the rejection. The response asserts that the data provided in the specification and the declaration determined that there was a significant relative risk associated with the presence of HapA and MI or stroke. The response, page 6, asserts that the invention relates to assessing the susceptibility of a human for developing MI or stroke. The methods are diagnostic screens and not diagnostic in themselves. The response cites many other unrelated examples suggesting the imperfections in diagnostic assays. This argument has been considered but is not convincing because the claims are drawn to "wherein the absence of the haplotypes identifies the individual as not having elevated susceptibility to MI or stroke." As discussed above in detail and argued by the response, other factors may cause susceptibility to MI and stroke. Thus the absence of the HapA haplotype does not indicate there is no susceptibility to MI or stroke. Alternatively, the data provided in the declaration does not appear to rise to the level of elevated susceptibility.

As specifically asserted by the response and in the declaration, 7 different populations were analyzed for the association between HapA and MI. The response asserts that the relative risk was greater than 1 for six out of seven populations. This argument has been reviewed but is not persuasive. A relative risk of 1 means there is

no difference in risk between the two groups. As a general rule of thumb we are looking for a relative risk of three or more [before accepting a paper for publication], particularly if it is biologically implausible or if it's a brand-new finding (see John P. A. Ioannidis (2005). "Why Most Published Research Findings Are False". *PLoS Medicine* **2** (8): e124.).

In the instant specification and declaration, the largest RR for the data given in Table 1 is 1.22. This RR is well below the recommended guidance provided in the art. Moreover, as seen in Table 1, the majority of the p-values for each association is greater than p=0.05. Specifically in a Phili group the p-value is 0.748; in a Clevland group p=0.057; in the United Kingdom p=0.211 and in Physicians health study p=0.058. It is noted that the Physicians study that applicant refers to in Table 1 actually reports much higher p-values in their Table 3. The P-values reported by Zee are 0.46 for US; ns for United Kingdome and 0.0001 for Iceland. Although the reponse asserts that "this data is stong evidence of reproducible and predictable results" the analysis does not appear to be signfiicant given the p-values greater than 0.05 and the relative risks not greater than 2 or 3. The results in the table appear to illustrate the further lack of association between various populations and HapA to MI as argued in the rejection above.

The response asserts that the LTA4H is distinct from the FLAP gene. This argument is persuassive, however, given the newly filed declaration and data, the ethnicity specificity is apparent given applicants own admission and the Zee publication cited in the Declaration.

The response asserts the Hirschhorn and Ioanniis caution against drawing conclusions from a single report. The response asserts that the instant application demonstrates the association in more than one population. This argument is not persuassive, given the data set forth in the Declaration. The Phili, Cleveland, Duraham, United Kingom and Physicians Health Study cohorts were not significantly associated. The only associations were found in Atlanta cohort and Iceland. This illustrates the unpredictability between populations and determining whether an association exists.

The response also argues that in the Hirschhorn studies 97 out of 166 assocaitiosn were observed in more than one study. This argument has been reviewed but is not persuassvive. This is a mere 58% of the time are the results of an association study correct. Morevoreve, Hirschhorn specifically states that only 6 of the associations have been consistently replicated, a meager 3.5%.

The response asserts, page 9 of the response, that additional data is provided to illustrate the relationship between HapA and MI. It is noted that no additional information about stroke has been provided.

The response argues the FDA approval standards. It is unclear why any argument toward FDA approval has been made. The standards and considerations for patenting and FDA approval are not coextensive. The requirements for a patent include enablement over the broad scope of the claims. Unlike, the assertions in the response, the data fails to provide a signficant association of HapA with MI or stroke.

Upon review of the declaration, the declarant indicates "I am a named co-inventor" however, this statement is confusing, as the declarant appears to be the sole

inventor. In the event that the declarant is a co-inventor, the inventors named on the patent should be modified.

Moreover, the declaration cites particualr Exhibitis, which do not appear to be provided in the instant response.

The declaration correctly states that no statistically significant association of HapA to MI and stroke was observed in British MI cohorts on page 91-92 of the specificaiton. The response appears to try to rely on an association of HapB and MI to support an association of HapA. HapB is a combination of SNPs namely SG13S377, SG13S114; SG13S41 and SG13S35. This is distinct from the instant claimed HapA and does not provide support for the claimed invention.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

7. No claims allowable.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
April 11, 2007